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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/938,406 | 08/21/2001 | George H. Lowell | 40646-2000210 | 1965 |

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| EXAMINER | |
|---|---|
| LUCAS, ZACHARIAH | |
| **ART UNIT** | **PAPER NUMBER** |
| 1648 | |

DATE MAILED: 08/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/938,406 | LOWELL ET AL. | |
| | Examiner | Art Unit | |
| | Zachariah Lucas | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3,4 and 6-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4 and 6-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Currently, claims 1, 3, 4, and 6-18 are pending and under consideration in the application.

2. In the prior action, the Final action mailed on November 16, 2004, claims 1, 3, 4, 6-18 were under consideration and rejected, and claims 2 and 5 were withdrawn as to non-elected inventions.

3. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 6, 2005 has been entered. In this submission, claims 2 and 5 have been cancelled; and claim 1 has been amended.

### *Claim Rejections - 35 USC § 112*

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. **(Prior Rejection- Withdrawn)** Claims 1, 3,4, 6, 7, 10-12, and 16-18 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite because it was unclear how a peptide can be "complexed" with a composition generally, rather than to elements within it (e.g. a bioadhesive nanoemulsion or proteosome). In view of the amendment of the claims to require that the complex is formed between the peptides and the bioadhesive nanoemulsion and/or proteosome, rather than between the peptides and the composition, the rejection is withdrawn.

***Claim Rejections - 35 USC § 102***

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. **(Prior Rejection- Withdrawn)** Claims 1, 3, 4, 6, and 10-17 were rejected under 35 U.S.C. 102(b) as being anticipated by Lowell et al., Science 240(4853): 800-02. The claims have been amended to require the presence of either 1) both a proteosome and a bioadhesive nanoemulsion, or 2) to require the presence of a bioadhesive nanoemulsion. Because such nanoemulsions are not disclosed by the Lowell article, the rejection is withdrawn.

8. **(Prior Rejection- Withdrawn)** Claims 1, 3, 4, 6, and 10-17 were rejected under 35 U.S.C. 102(e) as being anticipated by Lowell et al., U.S. Patent 5,726,292 (the 292 patent). The claims have been described above. The claims have been amended to require the presence of either 1) both a proteosome and a bioadhesive nanoemulsion, or 2) to require the presence of a bioadhesive nanoemulsion. Because such nanoemulsions are not disclosed by the Lowell article, the rejection is withdrawn.

***Claim Rejections - 35 USC § 103***

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. **(Prior Rejection- Restated and Maintained)** Claims 7 and 18 were rejected under 35 U.S.C. 103(a) as being obvious over the 292 patent as applied against claims 1, 3, 4, 6, and 10-17 above. Claim 1 has been amended as described above. In view of the amendment, the rejection is restated such that claims 1, 3, 4, 6, 7, and 10-18 are rejected over the teachings of the 292 patent in view of Anselem et al. (WO 94/26255). The teachings of the 292 patent have been described in part in the prior actions. It is noted that, among the routes of administration that the reference teaches were effective was the intranasal route (i.e. introduction to a mucosal surface). However, the reference does not teach, as asserted by the Applicant, the use of bioadhesive nanoemulsions.

The teachings of Anselem do provide for such nanoemulsions (see e.g., pages 5-6, and 24). Further, the reference teaches that the nanoemulsions disclosed therein may be used in combination with other adjuvant systems, including proteosomes. Page 8. Thus, it would have been obvious to those in the art to use the nanoemulsions disclosed therein either as a substitute for, or in combination with, the proteosome delivery system disclosed by the 292 patent. Anselem additionally teaches that the nanoemulsions may be formulated with bioadhesive additives to enhance delivery of antigens to mucosal surfaces. As the Lowell reference teaches the mucosal delivery of the indicated antigens was effective, it would have been obvious to use the bioadhesive nanoemulsions disclosed by the Anselem reference for the delivery of such

antigens. The combined teachings of these references therefore render the claimed inventions obvious.

11. **(Prior Rejection- Restated and Maintained)** Claims 7, 8, and 18 were rejected under 35 U.S.C. 103(a) as being unpatentable over Lowell as applied to claims 1, 3, 4, 6, and 10-17 above, and further in view of Vancott et al., J Immunol Methods 183: 103-17. The claims have been amended as described above. In view of the amendment to the claims, the rejection is withdrawn.

12. **(Prior Rejection- Restated and Maintained)** Claims 1, 3, 4, 6, 7, 8, 10, 11, 16-18 were rejected under 35 U.S.C. 103(a) as being unpatentable over any of the 292 patent, Lowell, or Lowell in view of Vancott as applied above, and further in view of WO 95/11700. The rejection is restated as a rejection over the teachings of the 292 patent or Lowell, in view of Vancott, and further in view WO 95/11700. The claims have been described above.

The Applicant traverses the rejection on several grounds. It is noted that the arguments provided by the Applicant with reference to the rejection including the teachings of Vancott (page 15 and 16 of the Response) will be addressed with reference to the present rejection. The arguments with reference to the Vancott reference are as follows: First, the Applicant asserts that the Vancott reference does not remedy the deficiencies of Lowell (re: the use of bioadhesive nanoemulsions). Second, the Applicant asserts that the Vancott reference does not provide "disclose the significance of hydrophobic peptide portions of oligomeric gp160 nor its complexing with either proteosomes or bioadhesive nanoemulsions." Third, the Applicant argues

that Vancott does not provide any particular teachings regarding a composition for inducing antibody formation. Fourth, the Applicant asserts that the reference teaches away from the use of truncated gp160 for the induction of antibody production. These arguments are not found persuasive.

The Applicant also provides a fifth argument in the form of an assertion in traversal of the present rejection that the nanoemulsion of WO 95/11700 is not a nanoemulsion according to the claims.

With respect to the teachings of the Vancott reference, the arguments are not found persuasive for the following reasons. The first argument is directed to asserted deficiencies of the rejection over the Lowell reference or the 292 patent. By this, it is assumed that the Applicant is referring to the absence of teachings regarding the use of bioadhesive nanoemulsions. The use of such emulsions have been described in the WO 95/11700 reference as previously described (and further discussed below). Thus, it the fact that neither Lowell, the 292 patent, nor the Vancott reference teaches their use is not found persuasive as such teachings are provided by the combined teachings of all of the cited references.

The Applicant's next (second) assertion is that the Vancott reference does not provide "disclose the significance of hydrophobic peptide portions of oligomeric gp160 nor its complexing with either proteosomes or bioadhesive nanoemulsions." The third argument is related to the second, in that it asserts that there is no specific suggestion in the Vancott reference to use the antigen disclosed therein in compositions for the induction of antibodies. The

teachings of Vancott provide other motivation for the use of this protein antigen- i.e. its ability to induce neutralizing antibodies. Regardless of the teachings of Vancott regarding the presence of the hydrophobic sequences, such sequences are inherent to that protein. Further, the teachings of the WO 95/11700 reference do specifically teach the use of the gp160 antigen with proteosome and nanoemulsion adjuvants. See e.g., pages 34-36. Based on the teachings in the WO 95/11700 reference, the gp160 antigen of Vancott would have been an obvious functional equivalent of the gp160 antigen in the WO document. Thus, the combined teachings of these references render obvious the use of the Vancott antigen in combination with the adjuvants formulations described by the other references. The failure to recognize any additional benefits of the native hydrophobic sequences in the gp160 does not render the claimed invention non-obvious. See, MPEP 2145 II. The cumulative teachings of the references provide other motivations for the combination, and specifically suggest the combination of gp160 with a nanoemulsion adjuvant. As such, the additional benefits of the claimed invention would naturally follow from the combined teachings of the Vancott reference and the WO 95/11700 reference.

The Applicant's fourth argument, the last directed to the teachings of Vancott, are not found persuasive because they are directed to an embodiment that is not directly rejected in the present claims. The truncated gp160 is the subject of claim 9, which was not rejected based on the teachings of the Vancott reference alone. With respect to those claims that were rejected, the argument is moot as directed to a limitation not present in the claims.

Furthermore, even with respect to claim 9, this claim is not limited to a truncated gp160 antigen. Rather, the claim is directed to antigen that "has the sequence of residues 33-681 of SEQ

ID NO: 1." The phrase "has the sequence" merely requires that this sequence is present, but does not exclude the presence of addition regions of the HIV gp160 protein. There is no limitation in the claim narrowing the claim to the asserted truncated gp160. Thus, even with respect to claim 9, the argument is moot as directed to a limitation not present in the claims.

However, if it is assumed that the claim was so limited, the following is provided in answer to the asserted teaching away of the Vancott reference. The Applicant asserts that the reference teaches that the V3 region of the gp120 protein is considered critical to the induction of neutralizing antibodies, and that the reference teaches that the truncated antigen would not be likely to elicit such antibodies. There is no support in the reference for these assertions. The Applicant points to the teachings on page 109 of the reference. While these teachings do relate in part to the V3 region of the antigen, the reference does not provide any teachings leading away from the use of the truncated antigen. Rather, the reference states that "Stronger binding against oligo-gp160(451) was obtained however this may be attributable to sequence diversity resulting in affinity differences rather than increased accessibility of the V3 loop within this protein." This statement teaches that the truncated antigen is more reactive to the neutralizing antibodies than the full-length antigen. Further, this statement clearly indicates that the V3 region is present in the truncated antigen. However, the reference provides no indication that the truncated protein would be ineffective as an anti-HIV antigen. Rather, the reference is merely unable to attribute the truncated antigens improved antibody reactivity with its truncated status. Thus, the reference indicates that this protein would be at least as effective an antigen as the full-length antigen.

For both of these reasons, the Applicant's fourth argument in traversal is not found persuasive.

The Applicant's fifth argument in traversal (presented cumulatively on pages 11 and 14 of the Response) is an argument referring to U.S. Patent 5,716,637- a related U.S. application to the WO 95/11700 reference. See, Response, pages 11-12. In this argument, the Applicant asserts that the structures included by the term "bioadhesive nanoemulsion" differ from the oil-in-water emulsions described by the WO 95/11700 reference. In support of this assertion, the Applicant notes that the application refers to the nanoemulsions of U.S. application 08/553,350 on page 37. This argument is not found persuasive.

WO 95/11700 teaches the use of oil-in-water submicron emulsions as a delivery vehicle that may also be used for the delivery of vaccines. Abstract. It is noted that other references in the art also refers to such oil-in-water submicron emulsions as nanoemulsions. See e.g., U.S. 6,303,150, column 2, lines 48-60. The Lowell PCT reference also teaches that such compositions may be used in combination with proteosomes, and may be formulated into bioadhesive nanoemulsions. See, page 4, lines 33-36; and pages 15-16. Additionally, the reference teaches a composition comprising the disclosed nanoemulsions with a complex or proteosomes and the HIV gp160 protein. Those of ordinary skill in the art would be motivated to combine the teachings of this reference with those of the other references in view of the teachings of the WO reference suggesting the combination of proteosomes and nanoemulsions, and by the teachings of both this reference and the 292 patent suggesting the combination of adjuvant formulation with the HIV gp160 antigen.

The Applicant's attempt to draw the distinction between the claimed nanoemulsions and those of the WO 95/11700 reference are not found persuasive because there is no definition in

the specification that limits the term bioadhesive nanoemulsion to the solid fat nanoemulsions of the 08/553,350 application. While the present specification refers to the nanoemulsions of U.S. application 08/553,350, it is also noted that the application (and the cited reference itself) refers to the nanoemulsions described by that application specifically as solid-fat nanoemulsions. App, page 37. See also, U.S. 5,716,637, the patent issued from U.S. application 08/553,350, at column 2 lines 44-53 (defining generally as being systems of one liquid dispersed in another); and col. 3, lines 8-11 (referring to the specific types of emulsions described therein as solid fat nanoemulsions or emulsomes). Thus, neither the teachings of the present application, or the application on which the Applicant relies to support their assertion, actually provides any support for the assertion that the generic term "bioadhesive nanoemulsion" refers only to the solid fat type nanoemulsions described in U.S. application 08/553,350. Applicant's attempt to argue that the WO 95/11700 reference is not art against the present claims is therefore not found persuasive.

For these reasons, and for the reasons of record, the rejection is maintained.

13. **(Prior Rejection- Reformed and Maintained)** Claim 9 was rejected under 35 U.S.C. 103(a) as being unpatentable over Lowell in view of Vancott as applied above, and further in view of Desai et al. (PNAS 83: 8380-84). The rejection is reformed as a rejection over 292 patent or Lowell, in view WO 95/11700, and further in view of Vancott and Desai. The Applicant traverses this rejection on the same basis as asserted with respect to the rejection

immediately above. For the same reasons as indicated above, these arguments are not found persuasive. The rejection is therefore maintained.

14. **(New Rejection)** Claims 1, 6-13, 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings either of Anselem or of WO 95/11700 in view of the teachings of Vancott and Desai. These claims have been described above. It is noted that the rejected claims do not require the present of the exogenous hydrophobic material. As previously described, each of the Anselem and WO 95/11700 references teach the use of nanoemulsions, including in combination with proteosomes, as adjuvants for the induction of an immune response against HIV gp160 antigens. See e.g., Anselem, pages 52-54; and WO 95/11700, pages 35-38. However, the references do not specifically teach the use of oligomeric forms of the gp160 proteins, or indicate that such proteins comprise the sequence of residues 33-681 of SEQ ID NO: 1.

The teachings of Vancott and Desai have been described previously. Vancott teaches that the oligomeric HIV gp160 antigen is effective for the induction of neutralizing anti-HIV antibodies. While the reference does not provide a specific sequence of such antigens, the additional teachings of the Desai reference does teach an HIV gp160 sequence comprising a region identical to residues 33-681 of SEQ ID NO: 1. From these teachings, it would have been obvious to those of ordinary skill in the art to use gp160 antigens as described in Vancott comprising the sequences disclosed in Desai in the immunogenic compositions described by either of Anselem or the WO 95/11700 reference. Those in the art would have had a reasonable expectation of success in the combination based on the suggestions in the primary references for

the use of the gp160 antigens with the adjuvant compositions in those references, and the teachings in Vancott with respect to the reactivity of the gp160 antigens with neutralizing antibodies. The combined teachings of the references therefore render the claimed inventions obvious.

***Double Patenting***

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. **(Prior Rejection- Maintained)** Claims 1, 3, 4, 6, 7, 10-18 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 5, 7, and 8 of U.S. Patent No. 5,726,292. The claims have been amended as described above. The rejection is therefore restated as a rejection of claims 1, 3, 4, 6-18 over claims 1, 2, 5, 7, and 8 of U.S. Patent No. 5,726,292, further in view of either of Anselem or WO 95/11700. In view of the teachings of these additional references as described above, the Applicant's arguments regarding the failure of the 292 patent to teach the use of bioadhesive nanoemulsions are not found persuasive. The rejection is therefore maintained.

17. **(Prior Rejection- Maintained)** Claims 1, 3, 4, 6-18 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 5, 7, and 8 of U.S. Patent No. 5,726,292 further in view of Vancott and Desai as applied above. The claims have been amended as described above. The rejection is therefore restated as a rejection of claims 1, 3, 4, 6-18 over claims 1, 2, 5, 7, and 8 of U.S. Patent No. 5,726,292, further in view of either of Anselem or WO 95/11700, and further in view of Vancott and Desai as described in the 103 rejection above. The rejection is therefore maintained for the reasons indicated above.

***Conclusion***

18. No claims are allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Z. Lucas
Patent Examiner

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8/19/05